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Dimethylsulfoxide–iodine catalysed deprotection of allyl carboxylic esters

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Abstract—A convenient method for deprotection of allyl carboxylic esters has been developed by using the inexpensive and environmentally friendly reagent dimethylsulfoxide–iodine. A variety of carboxylic esters were deprotected to the carboxylic acids. This method is more efficient and operationally simple in comparison to methods using transition metal complexes.

Carboxylic acids can be protected as anhydrides,[1] amides[2] or esters.[3] Allyl esters are particularly useful as protecting groups in carboxylic acids.[4] The allyl group has frequently been used in peptide synthesis as a protecting group due to its stability under basic, acidic and reduction conditions.[5] The allyl group for carboxylic acid protection is now generally used in the liquid or solid phase synthesis of a wide range of natural and synthetic products.[6]

Common allyl deprotection methods are two-step procedures that include isomerisation to the more labile 1-propenyl group with a variety of reagents. The most frequently employed conditions are treatment of the allyl carboxylic ester with palladium complexes[7] and the use of a stoichiometric amount of a nucleophile.[8] Complexes of nickel,[9] ruthenium[10] and rhodium[11] have also been used in deallylation procedures. The use of an excess of nucleophile, however, decreases the atom efficiency and sometimes causes problems during work-up. Most of these processes are slow. Palladium complexes have been reported to bring about decarboxylation–allylation in α-substituted β-keto-carboxylic acids and malonic, nitro and cyano acetic acids.[12a] Reaction of allyl α-fluoro-β-keto carboxylate with a Pd-complex gave α-fluoro ketones.[12b]

There has been a search for mild and chemo-selective reagents for the cleavage of allylic carboxylic esters. Schmidt reported that methyl, crotyl and cinnamyl esters were cleaved in refluxing formic acid whereas simple allyl esters were recovered unchanged under similar experimental conditions.[13] Iodine in cyclohexane at room temperature cleaved a prenyl protecting group but it did not cleave an allyl protecting group.[14] Similar observations were reported by Gajare et al., in the deprotection of allyl esters by K-10 clay under microwave irradiation.[15] This led us to utilise the inexpensive, readily available reagent iodine in dimethylsulfoxide for the deprotection of the allyl esters. The DMSO–I_2 reagent has been used in the oxidative cyclisation of 2′-hydroxychalcones to flavones[16] and the oxidation of flavanones to flavones,[17] isoxazolines to isoxazoles[18] and pyrazolines to pyrazoles.[19]

Earlier we reported our previous results on the deallylation of 2′-allyloxychalcones to afford flavones[20] (Scheme 1) in excellent yields. The deprotection products, 2′-hydroxychalcones, were not isolated since these compounds were immediately oxidised to flavones under these conditions.[21] In continuation of this effort, the present investigation describes a facile cleavage of allyl esters using the dimethylsulfoxide–iodine reagent (Scheme 2).

The method is applicable to allyl esters of both aromatic and aliphatic carboxylic acids. Allylic esters were prepared using conventional techniques (K_2CO_3, allyl bromide, DMF) in high yields. The allyl esters were then subjected to cleavage conditions, which involved heating

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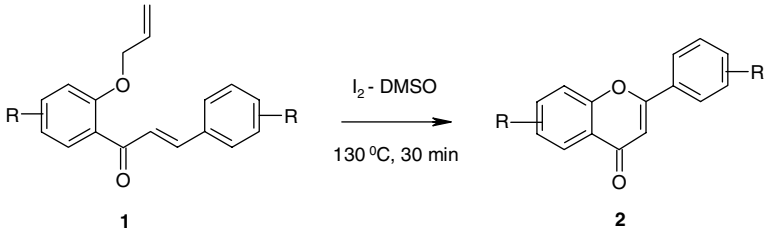


Scheme 1. Deallylation of 2′-allyloxychalcone.

Scheme 2. Deallylation of allylcarboxyl esters.

in dimethylsulfoxide with a catalytic amount of iodine and monitoring the reaction by TLC. The results are summarised in Table 1. The reactions were complete in 10–30 min at 130 °C. The allyl benzoates reacted slowly while allyl *p*-nitrobenzoate was deallylated in 20 min. A control experiment with ethyl benzoate demonstrated no cleavage under the reaction conditions, while allylmethyl salicylates and allyl aspirin ester resulted in the formation of salicylic acid. The effects of acid catalyst were also briefly investigated. In the presence of sulfuric acid (a catalytic amount), the reaction was found to be fast and was complete at 60 °C. This may be due to the inevitable presence of hydroiodic acid in the experiment, which hydrolysed the ester very rapidly. The allyl ester of ibuprofen was also cleaved smoothly. Protected allyl glycine, allyl phenyl glycine and allyl *p*-acetanilide carboxylate were also tested with this reagent and found to be deallylated smoothly.

Table 1.

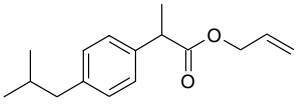
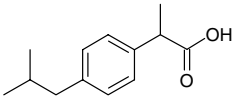
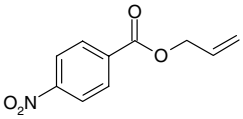
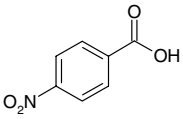
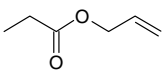
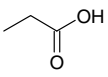
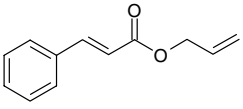
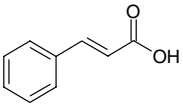
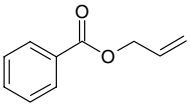
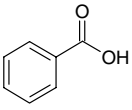
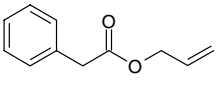
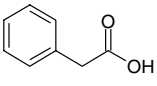
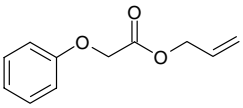
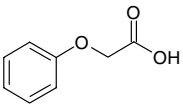
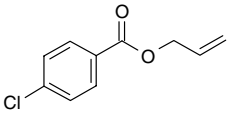
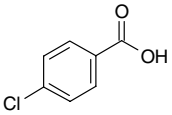
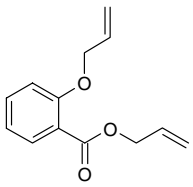
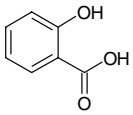
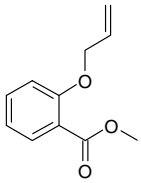
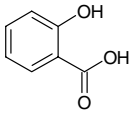
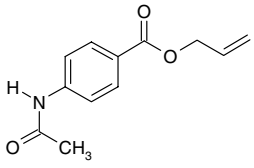
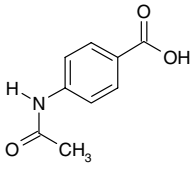
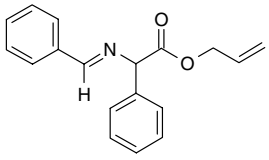
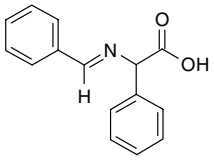
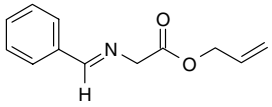
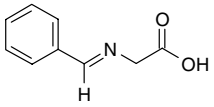
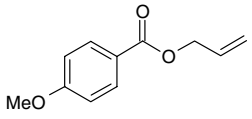
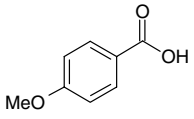
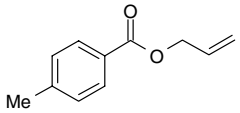
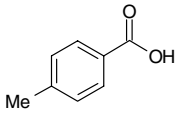
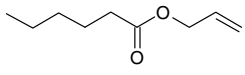
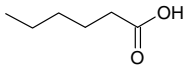
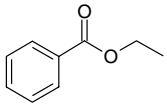
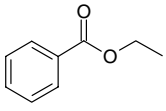
Entry	Reactant	Product	Time (min)	Yield (%)
1			30	71
2			20	95
3			8	73
4			20	87
5			30	90
6			30	85
7			30	80
8			12	76

Table 1 (*continued*)

Entry	Reactant	Product	Time (min)	Yield (%)
9			30	82
10			30	84
11			30	78
12			30	65
13			30	63
14			30	75
15			20	77
16			20	69
17			—	—

A range of various functional groups such as $–NO_2$, –OMe, Cl, —CH=CH— were compatible with the reagent. Groups like pyran,[22] methoxymethyl, β-methoxymethyl and methylthiomethyl were reported to be inert to iodine deprotection[23] and TBDMSCl[24] did not undergo deprotection in the presence of iodine under appropriate reaction conditions. In solvents other than dimethylsulfoxide including methanol, ethanol, diethyl ether, dichloromethane and benzene, the starting allyl esters were recovered. Thus the presence of both reagents, iodine in catalytic amount and dimethylsulfoxide, were necessary for the conversion of an allyl ester into a free carboxyl group. At temperatures higher than 155 °C it was observed that the >C=C< bond of 2′-allyloxychalcone was oxidatively cleaved to benzaldehyde. Therefore, the addition of an excess amount of iodine at higher temperature had to be avoided. In the absence of sulfuric acid at 100 °C, the reaction did not proceed.

Iodine is a soft nucleophile and prefers to react at the allylic position rather than at a carbonyl carbon. Sandhu and co-workers[25] reported that AlI_3 efficiently cleaved allyl carboxylic esters to carboxylic acids with iodine acting as a soft nucleophile. Iodine has been found to accelerate deallylation in the $(TBA)_2$ sulfate procedure for deallylation of allyl ethers.[26]

The present work provides an efficient and inexpensive deallylation procedure for a variety of allylic carboxylic esters. The reaction proceeds using a weak oxidising agent under neutral conditions in a short time. The ease of handling the reagent will encourage the use of allyl protection of carboxylic acids along with allyl phenol ethers.

The typical experimental procedure is as follows:

To a solution of allyl ester (207 mg, 1 mmol) in dimethylsulfoxide (3 ml) was added a catalytic amount of iodine. The reddish reaction mixture was heated in an oil bath at 130 °C for 30 min. After cooling, the reaction mixture was diluted with ice-cold water and the iodine was removed by the addition of a saturated solution of sodium thiosulfate and washing with water and brine. The product was extracted with ethyl acetate and washed with water. The organic layer was treated with a saturated solution of sodium bicarbonate solution, which dissolved the deprotected compound with strong effervescence. On neutralisation with dilute hydrochloric acid, the solid acid was isolated and purified by recrystallisation from a suitable solvent.

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